AD-A139 455 THE ROLE OF ENDORPHINS IN THE PATHOPHYSIOLOGY OF HEMORRHAGIC AND ENDOTOXIC SHOCK IN THE PRIMATE(U) IOWA UNIV IOWA CITY COLL OF MEDICINE* N J GURLL ET AL. 1/1

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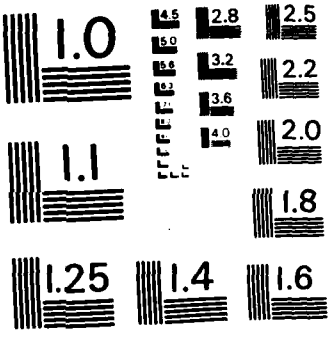

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REPORT NUMBER 1

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ANNUAL REPORT 1980-1981

NELSON J. GURLL, M.D., THOMAS VARGISH, M.D.,

AND DAVID G. REYNOLDS, Ph.D.

JULY 1981

SUPPORTED BY

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

FORT DETRICK, FREDERICK, MARYLAND 21701

CONTRACT NO. DAMD-17-80-C-0094

UNIVERSITY OF IOWA COLLEGE OF MEDICINE

IOWA CITY, IOWA 52242

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REPORT DOCUMENTATION PAGE

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1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A102 455
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle) THE ROLE OF ENDORPHINS IN THE PATHOPHYSIOLOGY OF HEMORRHAGIC AND ENDOTOXIC SHOCK IN THE PRIMATE	5. TYPE OF REPORT & PERIOD COVERED Annual Report 1 June 80 - 1 June 81
	6. PERFORMING ORG. REPORT NUMBER 1
7. AUTHOR(s) Nelson J. Gurll, M.D. Thomas Vargish, M.D. David G. Reynolds, Ph.D.	8. CONTRACT OR GRANT NUMBER(s) DAMD-17-80-C-0094
9. PERFORMING ORGANIZATION NAME AND ADDRESS University of Iowa College of Medicine Iowa City, Iowa 52242	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62772A.3S162772A874.AB.134
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Research and Development Command Fort Detrick Frederick, MD 21701	12. REPORT DATE July 1981
	13. NUMBER OF PAGES 16
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report) Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release - Distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

shock, endorphins, naloxone, hemorrhage, endotoxemia, primate shock, opiate receptors, pathophysiology of shock

20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In order to investigate the possible role and involvement of endogenous morphine-like substance (endorphins) in shock we studied cynomulgus monkeys subjected to hemorrhagic and endotoxemic shock. Blockade of opiate receptors with naloxone improved cardiovascular performance and survival in endotoxemic shock but produced only mild improvement in cardiovascular function and no increased survival in hemorrhagic shock. We conclude that endorphin systems are activated in and contribute to the cardiovascular depression in primate shock. Further work in this area is justified including development of a better primate hemorrhagic shock model.

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SUMMARY

In order to investigate the possible role and involvement of endogenous morphine-like substance (endorphins) in shock we studied cynomulgus monkeys subjected to hemorrhagic and endotoxemic shock. Blockade of opiate receptors with naloxone improved cardiovascular performance and survival in endotoxemic shock but produced only mild improvement in cardiovascular function and no increased survival in hemorrhagic shock. We conclude that endorphin systems are activated in and contribute to the cardiovascular depression in primate shock. Further work in this area is justified including development of a better primate hemorrhagic shock model.

FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BODY OF REPORT

a) problem. Shock due to hemorrhage and trauma is the most serious and lethal threat to the soldier in war. Even during peacetime septic and hemorrhagic shock are frequent and important conditions in military as well as civilian medical practice. These shock states do not always respond to appropriate therapies suggesting the possibility of other pathophysiological mechanisms and treatment modalities. Furthermore, the exigencies of the battlefield and rapid evacuation techniques favors the administration of specific anti-shock agents that don't require extensive preparation.

b) background. Endogenous opioids are elevated in the plasma during shock[1] and, like exogenous opiate compounds, depress cardiac function. The possible involvement of endorphin systems in shock was suggested by Holaday and Faden[2,3] and substantiated in rodent[2,3] and canine models[4,5] of hemorrhagic and endotoxemic shock. Blockade of opiate receptors with naloxone improves cardiovascular performance and survival in these models.[2-5] Preliminary clinical studies of naloxone in human shock have been encouraging but poorly controlled and generally unscientific.[6-9] In contrast to most species where adrenocorticotropin (ACTH) and β-endorphin rise and fall concomitantly,[1] steroids fail to suppress β-endorphin in humans and monkeys at doses that attenuate ACTH.[10] This suggests that endorphin control mechanisms are different in primates than other animals. For these reasons basic studies in primates are urgently needed.

c) approach. Cynomulgus monkeys were lightly anesthetized and instrumented to monitor mean arterial pressure (MAP), heart rate (HR), pulmonary arterial pressures, cardiac output (CO by thermal dilution) and left ventricular contractility (LV dp/dt max by differential amplification). Endotoxemic and

hemorrhagic shock were induced. Treatment with either naloxone 2 mg/kg i.v. bolus plus 2 mg/kg/hr i.v. infusion for 4 hours with 0.9% NaCl in equivalent volumes was begun when MAP reached 75 mm Hg after E. coli endotoxin 5 mg/kg i.v. In the hemorrhagic shock model the monkeys were bled to a MAP of 25-45 mm Hg which was maintained for 1-3 hours with an open reservoir system. The reservoir was then clamped and treatment begun with either naloxone 2 mg/kg/hr i.v. bolus plus 2 mg/kg/hr i.v. infusion for 3 hours or equivalent volumes of 0.9% NaCl. Shed blood was reinfused 1 hour later. The depth and duration of shock were modified (vide infra) because of problems with the original model.

d) results: hemorrhagic shock. In the first 14 monkeys we could find no difference in survival between naloxone (n=4) and saline treatment (n=10). These animals were unexpectedly non-acidotic despite MAP as low as 25 mm Hg. We discovered this was due to a factitiously low MAP because of large arterial pressure catheters relative to small femoral vessels. A smaller arterial pressure catheter inserted via the axillary artery gave accurate readings of MAP and were used subsequently.

In the next 19 monkeys the MAP was held at 30 mm Hg during shock with resultant acidosis and mortality in almost all. We were able to create a lethal shock model but were unable to demonstrate a beneficial effect of naloxone on survival. There was no statistically significant difference in survival rate or length of survival between naloxone (n=7) and saline treatment (n=12). This may be related to the acidosis which developed since acidosis decreases the binding of antagonists to opiate receptors. In the next 4 monkeys the depth of shock and the dose of naloxone were modified so that survival would be improved. We finally were able to achieve a shock

model with partial survival using a MAP of 45 mm Hg and a naloxone dose of 2 mg/kg plus 2 mg/kg/hr.

In the subsequent 10 animals studied under these conditions there again was no difference in survival between naloxone (n=5) and saline (n=5). Taken as a whole, there were no differences between treatment groups in survival, but naloxone did produce some improvement in MAP, CO, and LV dp/dt max in some of the 21 animals treated. The response to naloxone was "good" in 2, "moderate" in 3, "slight" in 3, transient in 5, and absent in 8 animals. Four of the 8 without responses to naloxone had catheter injuries to the heart, a problem found in 6 of the 49 monkeys studied in hemorrhagic shock. Two monkeys died of this catheter-induced injury before being randomized to any treatment group.

e) results: endotoxemic shock. Twelve monkeys were studied. Survival rate was significantly better in the naloxone treated group (6/6) than in the saline treated group (1/6, $p<.01$ by Fisher's exact test). Naloxone significantly improved MAP by 25-30 mm Hg over saline treated controls ($p<.02$ by ANOVA, Figure 1). LV dp/dt max was higher in naloxone treated monkeys (3600 mm Hg/sec) than in controls (2400 mm Hg/sec), a difference that was highly significant statistically ($p<.01$ by ANOVA). There were no differences between naloxone and 0.9% NaCl with respect to CO, stroke volume, HR, peripheral vascular resistance, body temperature, and metabolic measurements. Naloxone improved LV dp/dt max by 800 mm Hg/sec compared to no change with saline ($p<.02$ by ANOVA, Figure 2).

f) results: hormones and neurohumors. There was no significant elevation of plasma histamine in response to the shock states. Plasma assays of β-endorphin, cortisol, and ACTH will be done presently. No results, even preliminary, are available.

g) discussion. The results in the endotoxemia study suggest that endorphin systems are activated in and contribute to the cardiovascular pathophysiology of endotoxemic shock in primates. Furthermore, our results suggest the feasibility of using naloxone in shock states due to sepsis and endotoxemia. The dose of 2 mg/kg plus 2 mg/kg/hr is effective in converting an 80% lethal model to 100% survival. The possibility of using lower doses might be considered.

The results in hemorrhagic shock are not nearly so encouraging but may reflect deficiencies in the model and not in the concept. There are some cardiovascular responses to naloxone which suggest that some of the cardiovascular depression is due to endorphins acting on opiate receptors (since naloxone has no effect in non-shock states).[4] Deficiencies in the model and in the dose of naloxone used may be clarified by the plasma β-endorphin results especially comparing the different shock models.

Failure to demonstrate increased plasma histamine in shock suggests that this compound does not contribute to the cardiovascular abnormalities found. Because of its rapid metabolism it still might be released by endogenous opioid substances.

h) conclusions. Endorphin systems are activated in shock, especially endotoxic shock. Beneficial cardiovascular effects accrue from blockade

of opiate receptors with naloxone leading to prolonged survival at least in the endotoxemia model.

i) recommendations. Hemorrhagic shock is obviously of prime importance. Further work on the primate shock model is needed, the direction of which may be a function of the plasma β-endorphin levels. If β-endorphin levels are elevated in the endotoxemic but not the hemorrhage model then a more severe hemorrhage model is needed. If β-endorphin is elevated in both models then one should address the problem of naloxone dosage in hemorrhage. If plasma β-endorphin is not elevated in either model or normal in endotoxemia while elevated in hemorrhage then more consideration ought to be given to central nervous system endorphin systems (met-enkephalin, leu-enkephalin, hypothalmic β-endorphin) than pituitary endorphins in shock.

These preliminary results are exciting and warrant further work: 1) developing the hemorrhagic shock model, 2) looking at mechanisms involved and 3) exploring the use of non-opioid opiate antagonists like thyrotropin releasing hormone. The use of primates is mandatory.

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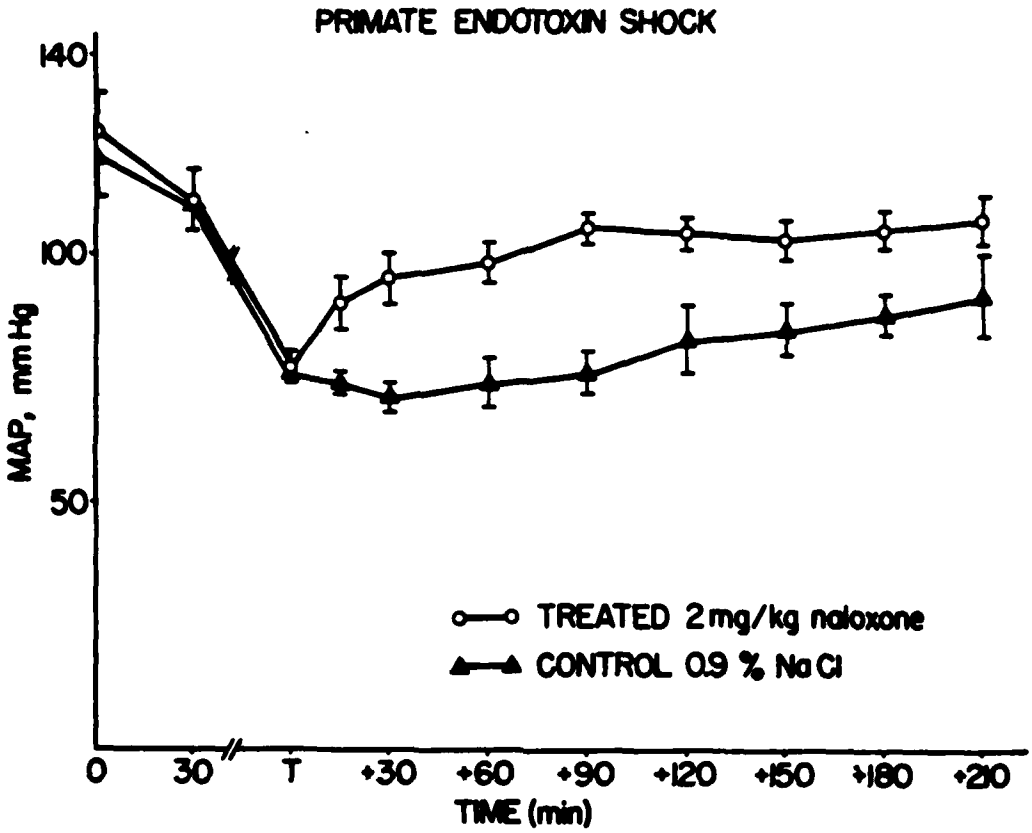
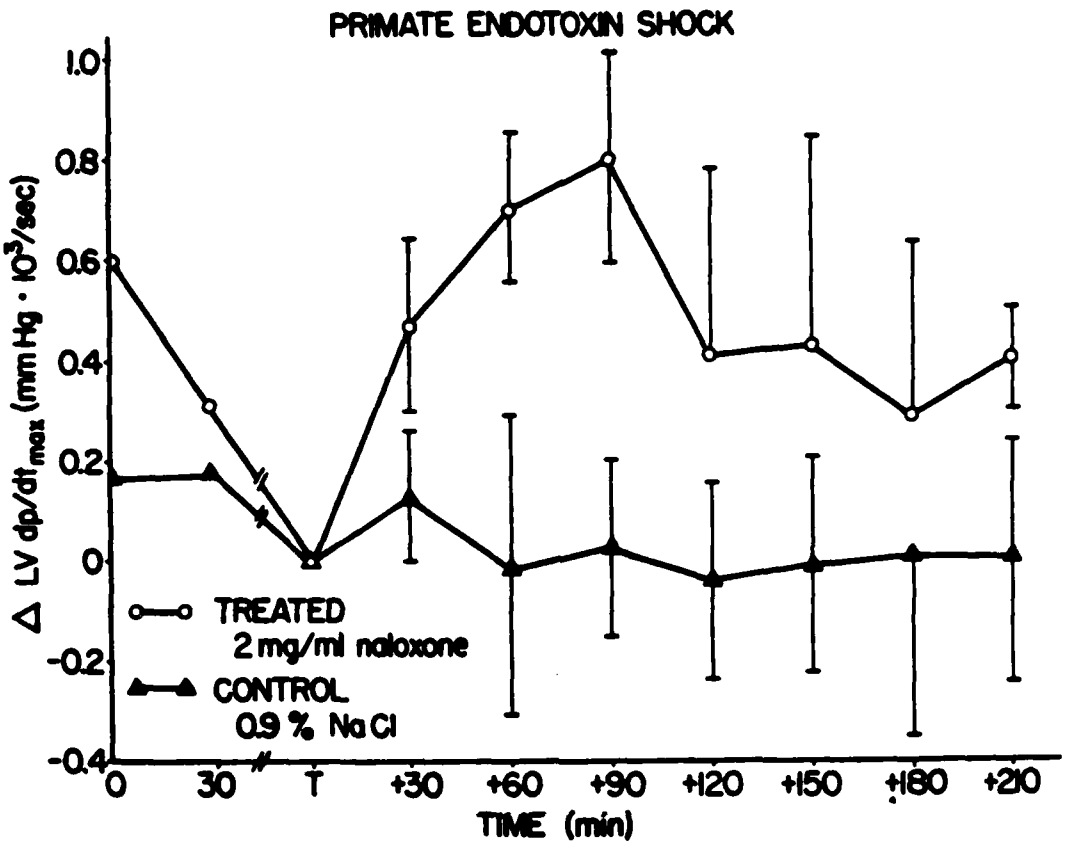
APPENDICES

Figure 1. The response of mean arterial pressure (MAP, mm Hg) to naloxone 2 mg/kg plus 2 mg/kg/hr i.v. versus 0.9% NaCl in cynomulgus monkeys given E. coli endotoxin 5 mg/kg. Treatment begun when MAP reached 75 mm Hg. (time t=0). Results are shown as mean ± SEM.

Figure 2. The response in left ventricular contractility (LV dp/dt max, mm Hg x 10^{-3}/sec) to naloxone versus 0.9% NaCl in monkey endotoxemic shock. See legend of Figure 1 for details.


PRIMATE ENDOTOXIN SHOCK
140
100
50
MAP, mm Hg
TREATED 2 mg/kg naloxone
CONTROL 0.9 % Na Cl
0
30
T
+30
+60
+90
+120
+150
+180
+210
TIME (min)


PRIMATE ENDOTOXIN SHOCK
1.0
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Δ LV dp/dt max (mm Hg · 10³/sec)
TREATED
2 mg/ml naloxone
CONTROL
0.9 % NaCl
0
30
T
+30
+60
+90
+120
+150
+180
+210
TIME (min)

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